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REVIEW ON OCCULAR IONTOPHORESIS: DRUG DELIVERY SYSTEM & RECENT CLINICAL APPLICATION

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❖ Abstract:

"VISION 2020, THE RIGHT TO SIGHT" was a global initiative launched in 1999. Drug delivery to theinner eye is still a challenge in ocular therapy. Current the administration of drugs for the treatment of eye diseases is mainly carried out using solutions, ointments and suspensions. These systems are relatively ineffective as drug delivery systems; often just 1% of the available drug is absorbed by the eye. Ocular iontophoresis is a non-invasive technique which provide a convenient way of administration for many therapeutic indications. This review highlights the basic concept of ocular iontophoresis, iontophoretic devices, trans corneal and trans cleral iontophoresis of various drugs with an emphasis on applied current density and duration of treatment used by investigators.

❖ **Keywords:** Iontophoresis , cornea, Iontophoresis applicator ,noninvasive, emphasis, transcorneal .

❖ Introduction:

Iontophoresis simply defined as the application of an electric potential which maintains a

constant electric current across skin and increases the supply of ions as well as unionized groups. It's a drug applied non-invasively with an electrode carrying the same charge as a drug, a ground electrode, which is the opposite charge, is located elsewhere on the body to complete the circuit. The drug serves as a tissue current conductor. This technique is able to expand the range of compounds that can be supplied locally. Along with the benefits bypassing the effect of the first pass of the liver and higher patient compliance, other benefits of iontophoretic techniques are, It is a replacement for chemical amplifiers. It eliminates that associated adverse reactions and toxicity the presence of chemical enhancers in pharmaceutical formulation. It required less amount of drug compared to conventional system for local drug delivery. Drug delivery to the inner eye still represents a critical eye problem therapeutics. Deep eye fluids and tissues cannot be effectively achieved by current administration while eye medication administered systemicallyhave bad accessibility to the inner eye due to blood aqueous and blood retinal barriers.

Subconjunctival and retrobulbar injections yes do not produce adequate levels of th drug while directly intracameral or intravitreal administration, which is invasive procedure can lead to serious intraocular complications. iontophoresis, which consists in the application of a weak electric current to drive charged drug molecules through tissue barriers, is one of the proposed alternative delivery techniques therapeutic doses of medication into the inner eye. Ocular Iontophoresis was first investigated in The German investigator Wirtz in 1908, who an electric current passed through the electrolyte saturated cotton sponges placed over globe for the treatment of corneal ulcers, keratitis and episcleritis. Even century, iontophoresis was widespread investigated for supplying eye medication, including dyes, antibacterial, antiviral, antifungals, steroids, antimetabolites and even genes. A literature survey shows that not much current densities, iontophoresis is safe and does not cause any structural changes cornea. That's what eye iontophoresis seemed like be an alternative to low bioavailability of drugs after topical administration and to potential serious complications after intraocular injections used for treatment many eye disorders. Instead of its extended use and study during the first 60 years 20th century iontophoresis never was fully customized as a standard procedure. Lack of carefullycontrolled trials and shortages Toxicity data was one reason precluded its adoption as analternative to drug delivery. However, the last ten years they have seen development and optimization ocular iontophoretic technologies for rapid and safe delivery of high drug concentrations in a specific eye location. Current review discusses the basic concept, recent development and results of the study in ocular iontophoretic field. BASIC CONCEPT OF IONTOPHORESIS.

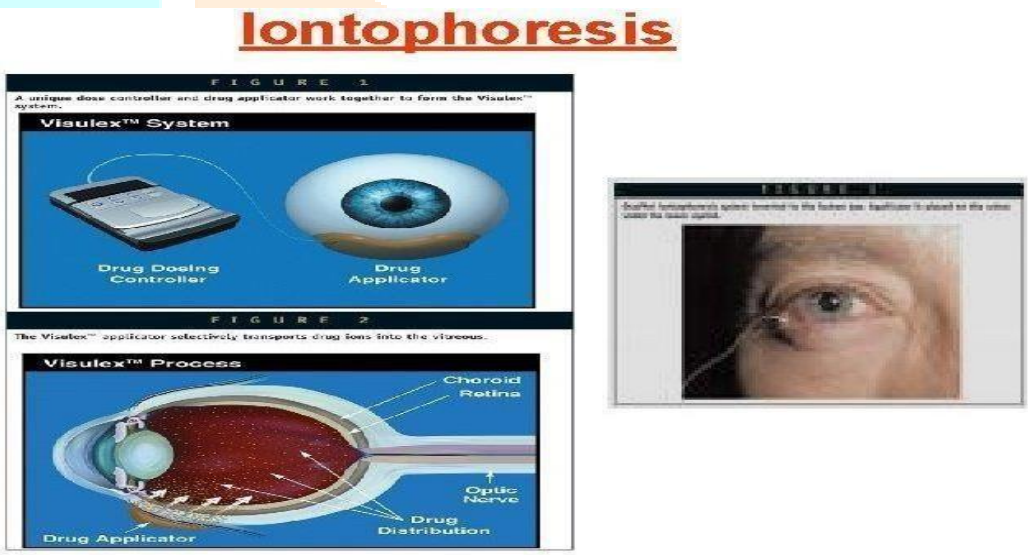


Fig 1: Advance in ocular Iontophoresis

❖ Basic concept of Iontophoresis:

The iontophoretic technique is based on the general principle that similar charges repel everyone other. That is, during iontophoresis, if supplied a positively charged drug is desirable the chargeddrug dissolves in the electrolyte surrounding an electrode of similar polarity, i.e. the anode in this example. On application of the electromotive force of the drug it is repelled and moves across the eye barrier towards the cathode which is placed elsewhere on the body. Communication between the electrodes along the surface has turned out to be negligible, i.e. movement ions of the drug occur between the electrodes by eye and not on the surface. When the cathode is located in the donor separation of the Franz diffusion cell to to increase the flow of anion, it is called cathode iontophoresis and vice versa. It has been observed that neutral molecules move by convection currents due to electro-osmotic and osmotic forces in application electric current. Electromigration of ions during iontophoresis causes convective solvent movement and this solvent movement in turn "pulls" neutral or even charged molecules along with that. This process is called electro-osmosis. If there are any neutral drug molecules present at the anode at this time may be transported through the eye along with water. Such movement of water often results in anode pore shrinkage

and pore swelling on the cathode. Nernst-Planck equation was used with modifications to predict iontophoretic enhancement ratios (ratio steady flow in the presence of elpotential and in the absence of potential) as the original equation lacks a term for convection electroosmotic flow. Increased flow during iontophoresis would include

1. Flow due to electrochemical potential gradient across the skin.
2. Change in eye permeability as a result applied electric field.
3. Electroosmotic flow of water the resulting solvent resistance.Jionto = Jelectric + Jpassive + Jconvective

Jelectric is a flow caused by an electric current application; Jpassive is the flow caused by the passive delivery through the skin; and Jconvective is flow due to convective transport due to elecosmosis.

❖ The Iontophoresis device:

Essentially, iontophoretic devices consist of continuous direct current source and two electrodes. The the ionized drug is placed nearby electrode space bearing the same charge and the ground electrode is placed on elsewhere on the body surface. They exist two approaches for drug retention in iontophoretic device. Most often the approach used is to fill the eye cup drug solution, while the metal electrode extended from current supply dives into the solution. Orbitalsand inner diameter of 5–10 mm is placed above eye and the drug solution is continuously infused into the cup during iontophoresis therapy. The eye socket has two ports: one delivers the drug solution and the other holds metal electrode and sucks in air bubbles which may disrupt the current supply which creates a slightly negative pressure which keeps the applicator in place. Earth the electrode is usually placed near the ear animal as close as possible to the first electrodesto have minimum resistance. Eye-cup of various shapes, contains an a ring-shaped silicone probe that is used for transscleral iontophoresis (called Eyegate, Optis, France) with a 13mm hole to avoid corneal contact, used by Voigt ,Hayden and BeharCohen .The second approach is a delivery probe containing a drug-saturated gel. Jones a Maurice first used this method for delivery fluorescein into the anterior chamber eyes using a fluorescein-saturated agar gel. The gel was filled into a plastic tube and was partially extruded from the tube to form a straight contact withthe eye. Later Grossman and Frucht-Pery used the same concept with gentamicin saturated agarfor transcorneal and transscleral iontophoresis in rabbits.

However, the use of agar was unacceptable because the agar material was brittle and left over agar residues on the surface of the eye that were visually disapproved. In the current scenario, loaded with drugs hydrogels for ocular iontophoresis revealed new iontophoretic applicators using drug-saturated gel approach. Fisher, Vollmer and Parkinson et al. used custom produced OcuPhori hydrogel (Iomed Inc, Salt Lake City, USA) composed of polyacetal sponge, for transscleral iontophoresis. The medication applicator is a small silicone shell which contains patented silver chloride ink conductive element; hydrogel pad absorb the dosage form; and small flexible wire for connecting the conductive element to the dose regulator. During administration is a dry hydrogel matrix hydrated with a drug solution and placed against the sclera in the lower cul-de-sac rabbit eye. The return electrode is placed elsewhere on the body to complete electrical circuit. The analog applicator was developed and reported by Visulexi (Aciont Inc., USA), Hastings and Li for ophthalmology applications. Visulexi has developed a unique selective membrane thatincreases the drug transport by creating drug ions as primary carrier of electric current to the sclera tissues and exclude the transport of non-medicinal substances ions. Frucht-Pery and Eljarrat-Binstock et al used a portable iontophoretic device containing polyacrylic porous hydrogel saturated with dexamethasone or gentamicin solution for transscleral and transcorneal iontophoresis. The hydrogel is placed in a the well that is at the tip of the electrode a placed on the eye. Use a A hydrogel applicator appears to be advantageous it is convenient, less harmful tothe eye surface, it experiences minor blackouts compared to the eyeball.

❖ Evolution of Trans-scleral Corticosteroid Delivery Using Iontophoresis:

Over the past 2 decades, advances have been made in the transscleral field administration of corticosteroids has evolved through preclinical research, early human experience and development in iontophoresis delivery systems. An early preclinical study in rabbits used coulomb controlled iontophoresis system with silicone applicator designed to closely fit the contour of the rabbit's eye administer methylprednisolone hemisuccinate (HMP).28 Ocular layer of methylprednisolone levels were compared HMP via iontophoresis or intravenous administration her. After iontophoresis, the concentration of methylprednisolone solitary increase in all ocular tissues (cornea, iris/ciliary body, sclera, choroid and retina) and fluids

(aqueous solution and vitreous) tested in relation to the current intensity bindings used. Iontophoresis was achieved higher and more permanent tissue concentrations of methylprednisolone than intravenously administration, with minimal systemic absorption and no eye complications. Preclinical studies using transscleral cathode iontophoresis of dexamethasone phosphate resistance (10, 20, 30 mA-min) in rabbits achieved significantly higher levels of dexamethasone and dexamethasone phosphate in aqueous humor, vitreous humor, choroid, andretina of the rabbit eye than levels of pro-induced by passive diffusion (ie eye drops).29 Specifically concentration of dexamethasone in aqueous humor postiontophoresis was 50- to 100-fold greater than that reported elsewhere after topical instillation of 0.1% dexa-metasone phosphate in the same rabbit strain (two 25ml drops 5 minutes apart),30 and vitreous concentration significantly exceeded levels considered sufficient for replenishment pressing inflammatory processes.Furthermore, once every two weeks transscleral iontophoresis dexasolution of metasone phosphate in current doses of 10, 14 and 20 mA-min for 24 weeks appeared to be safe in rabbits, with a no treatment-related effects on intraocular pressure (IOP), electroretinography, or any histopathology. Therapeutic use of iontophoresis devices (EyeGate Pharmaceuticals, Inc., Waltham, MA) to supply corticosteroid was originally clinically investigated in 17 patients who there was active rejection of the graft after penetrating keratoplasty. Iontophoretic applications of 62.5 mg/ml pervitinylprednisolone sodium succinate was administered once daily for 3 consecutive days using an electric current of 1.5 mA for 4 min. After treatment complete rejection rejection process was achieved in 15/17 (88%) treated eyes and no significant side effects were observed, including the absence of steroids induced increase in IOP. Hypothetically, the lack of IOP leakage may be due to the "pulse" nature of the steroid delivery by iontophoresis. These findings supported the feasibility of using iontophoresis to treat inflammatory eye disease. In the years from dexamethasone phosphate has been shown to be a key molecule in transscleral iontophoresis studies based on physicochemical properties that make it favorable for iontophoresis (i.e solubility in water, 2 negative charges at physiological pH). EyeGate II Delivery System (EGDS; EyeGate Pharmaceuticals, Inc.) is a proprietary transscleral iontophoresis system designed to non-invasively deliver drug to posterior eye segments. When current is applied to the electrode located in the ring eyepiece applicator, the electrode produces ions that propel the ionized of drug molecules via electrochemical repulsion through conjunctiva and sclera . This system achieves substantial drug levels in ocular tissues while minimizing systemic exposure and has been used in conjunction with EGP-437, Dexamethasone Phosphate 40mg/ml specified formulated for iontophoretic delivery.

❖ **Clinical studies of Iontophoretically delivered corticosteroid in Ocular inflammatory diseases:**

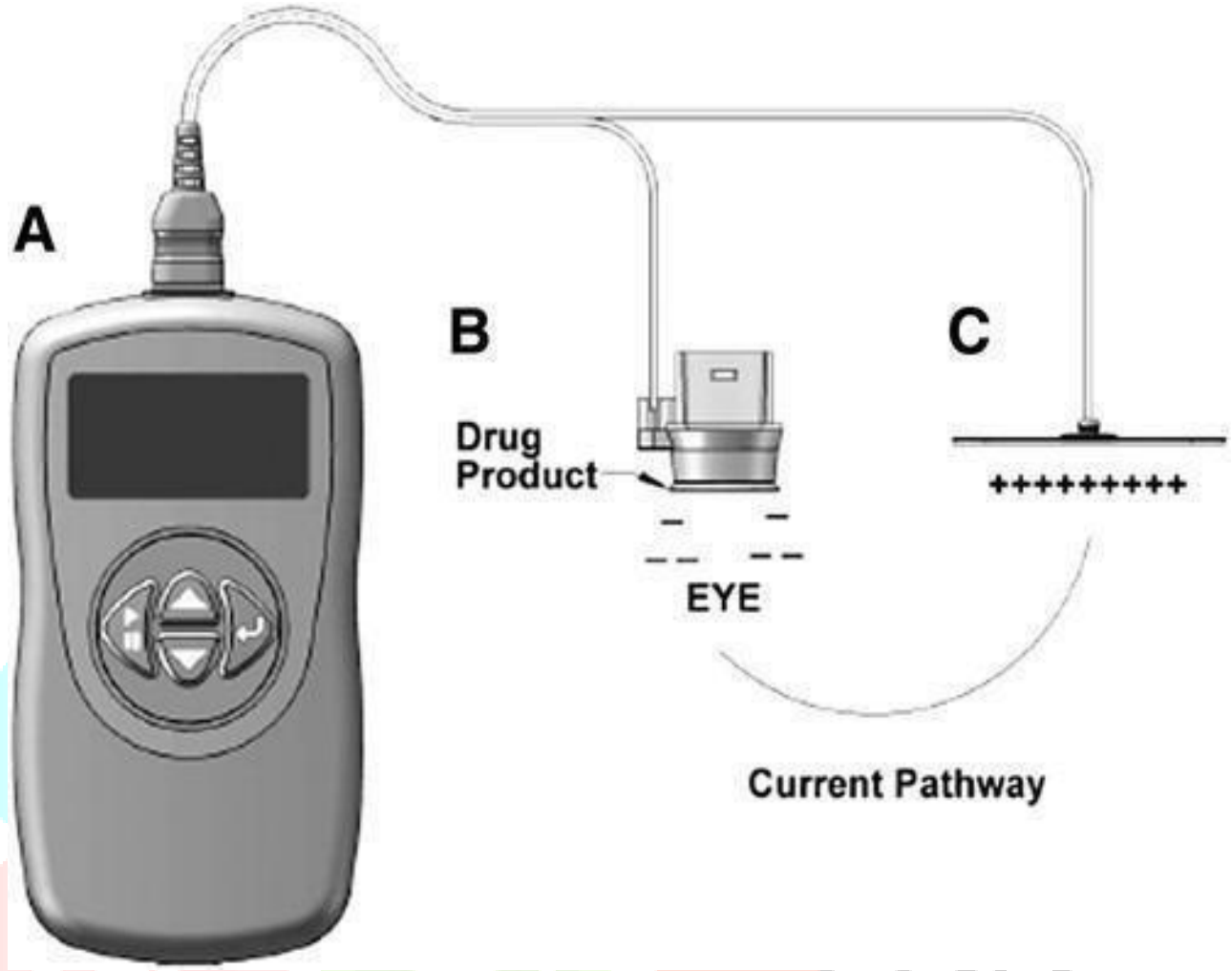


Fig2: EGDS configuration for cathode iontophoresis dexamethasone. System components include the following: (A) a generator that supplies constant current to the application cator electrodes (iontophoresis unit EGDS) and displaysreal-time current delivery, delivered dose and remaining amount time in treatment; (B) ring eye applicator containing an inert chemical electrode and a hydrophilic a foam reservoir that holds *0.5 ml of medicinal product solution; (C) a return electrode that allows current to pass from the patient and back to the constant current generator and is placed on the forehead; and (not shown here) a transfer system consisting of a syringe and a tip, ex, transfer the medicine from the bottle to the foam medicine container applicator. EGDS , Eye Gate II delivery system.

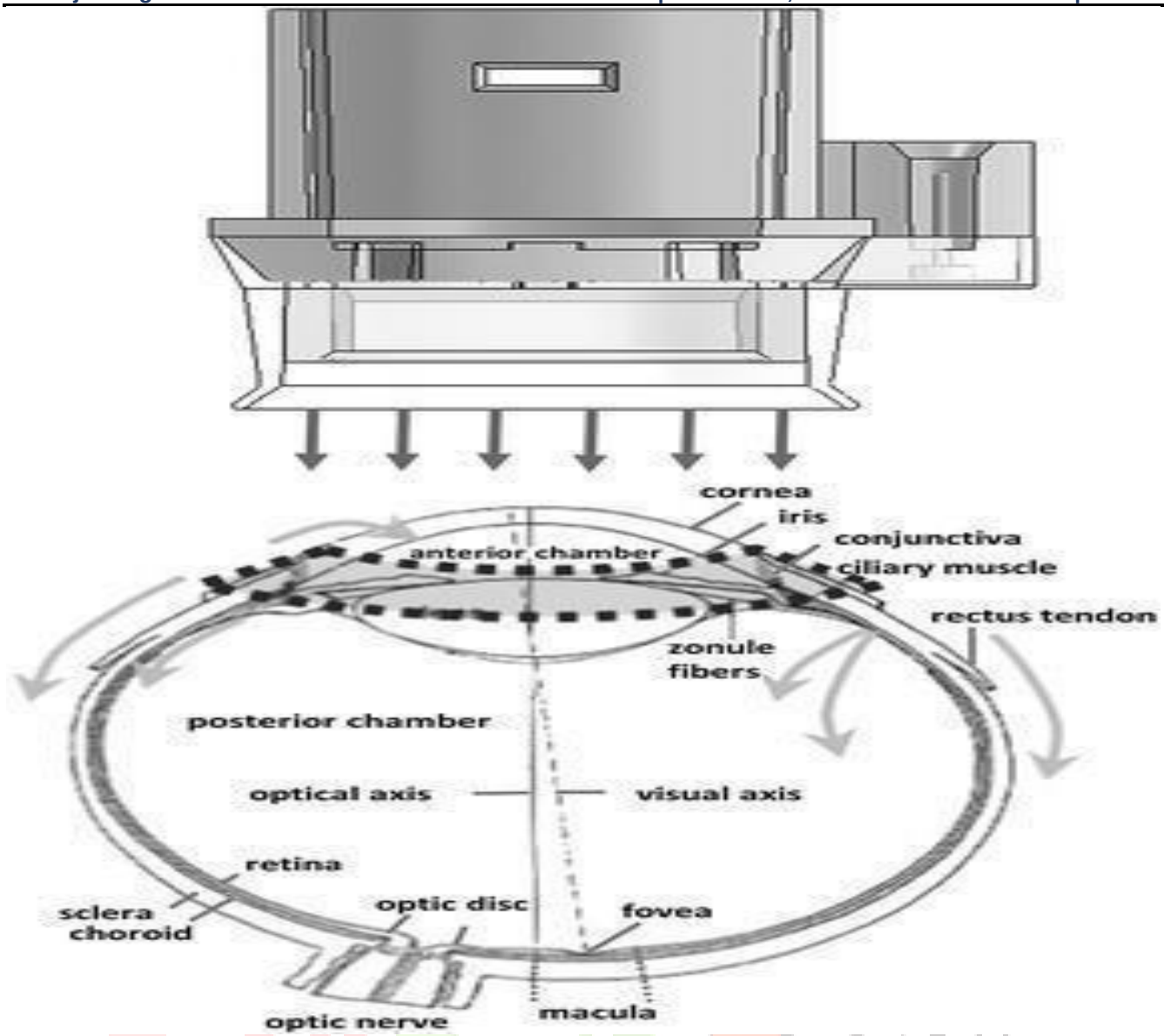


Fig3: Delivery of dexamethasone to the eye using EGDS. Fifteen minutes after the transscleral iontophoretic dose dexamethasone most of the dexamethasone is found in anterior segment tissues (red zone). Then the part dose of dexamethasone may diffuse back into the water humor AC or diffuse posteriorly into and through sclera, choroid and vitreous. AC, anterior chamber. administration of steroids in formal clinical trials for eye disease associated withinflammation, including active graft rejection, anterior uveitis, dry eye, postoperative inflammation and pain, and noninfectious, necrotizing scleritis.

❖ Transcorneal iontophoresis:

Transcorneal iontophoresis was used in order to deliver a high concentration drug into the anterior segment of the eye (cornea, aqueous humor, ciliary body, iris and lens), for the treatment of the anterior segment diseases such as: glaucoma, dry eyes, keratitis, corneal ulcers and eye inflammations. Fishman reported that transcorneal iontophoresis does not have the potential topenetrate a drug into the posterior segment of the eye as a result lens barrier unless aphakic rabbits used. For the treatment of corneal ulcers transcorneal iontophoresis of antibiotics appears to be a potentially effective method.

The literature survey shows successful penetration of antibiotics into the anterior part chamberafter iontophoretic treatment, as compared to topical instillation of eye drops drug . Efficiency treatment was investigated in the eyes of rabbits after pseudomonas intrastromal injection.

Gentamicin, tobramycin and ciprofloxacin Iontophoresis has been shown to have a drastically lower bacterial colonies in the cornea compared with frequent dripping of eye drops.

Vancomycin, complex glycopolypeptide antibiotic, resulted in poor corneal penetration compared to others antibiotics, due to its high molecular weight (1448 Daltons). Iontophoresis significantly improves penetration of vancomycin, which resulted in effective delivery of the same.

Steroids are misdiagnosed for the transcorneal route despite the fact that dexamethasone assumes have much higher corneal penetration than positively charged antibiotics application ofcorneal iontophoresis . Although these relatively successful transcorneal results iontophoresis has never been studied randomized, controlled trials. The reason may be common local drops instillation is relatively successful in treatment most anterior eye disorders, although it requires frequent dosing but has very little complication.

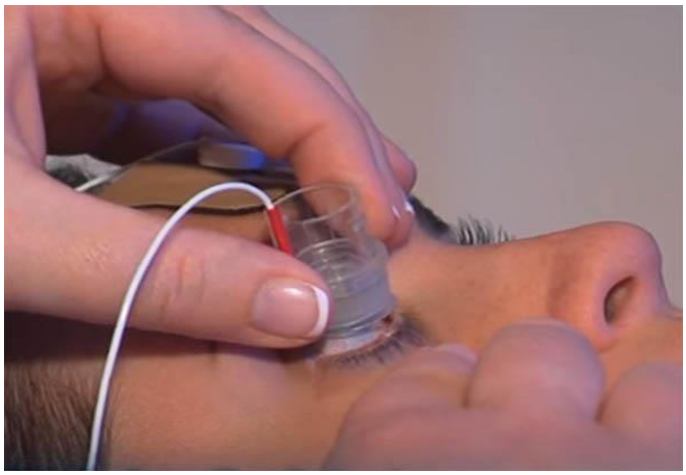
❖ Mechanism of action:

The process of iontophoresis involves the application of electricity. The current on an ionizable substance to increase its surface mobility, a concept that extends to 18th century. The first transscleral iontophoretic application cation for vitreous drug delivery has been reported in 1943.

David Maurice later starred role in the development of the use of iontophoresis to improve the administration of drugs into the eye, but techniques for ophthalmic iontophoresis have development took decades. Although scientists engineers and ophthalmologists have experience mented by a wide variety of ocular ionstophoresis devices and drugs, no product has approved, nor was data available published from carefully controlled clinical trials dealing with the efficacy and safety of this delivery method. During the past decade, however, technology has advanced significantly abrupt and equipment can quickly and safely deliver high drug concentrations to theeye tissues.

Many reports describe examples of ocular iontophoresis yields significantly higher ocular drug concentration than traditional current application. A new system of ocular iontophoresis, EyeGate II Delivery System (EGDS; Eyegate Pharmaceuticals, Inc., Waltham, MA). have been designed to achieve an optimal therapeutic effect front and rear drug levels segments of the eye, while at the same time minimizing system distribution. EGDS uses an inert electrode, which electrolyzes water to form hydroxide or hydronium ions needed to propel charged drug molecules. Iontophoretic delivery of anionic drug during physiological pH requires cathodic electrolysis with EyeGate inert electrode. This process generates accepts hydroxide ions that promote movement of anion into the eye tissues, while currently increases the pH of the drug solution.

Fig 4: occular applicator place on eye



With the reverse strategy, iontophoresis cationic drug delivery at physiological pH requires anodic electrolysis with Eye Gate inert electrode. This process creates hydronium ions which promote the movement of the cation into the eye tissue while lowering the pH of the drug solution. In both strategies, it contains a solution of the medicinal product sufficient buffer capacity to accommodate generation hydroxide or hydronium ions.

❖ Eye irritancy study:

Iontophoresis is a local non-invasive technique administration associated with min discomfort for the patient. However, this the procedure can lead to complications such as epithelial edema, decrease in endothelial cells, inflammatory infiltration and burns. Such damage depends on the site of application, current density and iontophoretics duration. Transcorneal and transscleral iontophoresis results under the same conditions in different levels of toxicity due to significant differences between corneal tissue and sclera.

Any damage to the corneal surface immediately affects the patient's vision and comfort which is less severe when applied to the sclera. Corneal clarity is essential for interaction with light, while the sclera does not relevant to the interaction of light. The cornea is an avascular and highly innervated tissue, not as sclera, i.e. very sensitive to pain and hypoxia. Transcorneal on one side iontophoresis threatens the front window ocular but on the other hand transscleral iontophoresis threatens the retina underneath place of application that is necessary for creating a visual image. This section discusses literature related to iontophoretics eye toxicity when applied to the cornea or on the sclera.

Transcorneal iontophoresis was evaluated for potential corneal toxicity Hill et al, showing minimal surface pitting of the cornea immediately after applying a current of 0.5 mA for 4 min. Huges and Maurice applied current densities of 20–25 mA/cm2 for 1 and 5 min above the diameter of 4 mm polyacrylamide gel discs lying over the cornea rabbits. They observed fluorescein staining epithelium and mild stromal swelling cornea immediately after treatment which return to normal after 24 hours. Nothing serious Endothelial damage has occurred, confirmed immediately scanning electron microscopy after treatment 24 and 48 hours after. Choi and Lee achieved 8.8% and 5.4% respectively. a decrease in the number of endothelial cells 4 days after vancomycin transcorneal iontophoresis a saline or current density 7.1 mA/cm2 for 5 min. Rootman et al found minimal abnormalities of the surface epithelium using light and electron microscopy, immediately after 0.8 mA/cm2 transcorneal iontophoresis for 5 minutes and focal areas epithelial edema after 10 minutes of iontophoresis. The stroma and endothelium remained normal. Grossman and Lee reported. persistent corneal opacity after transcorneal ketoconazole iontophoresis using high current density 21 mA/cm2 for 15 min. Grossman demonstrated corneal toxicity 3 days after gentamicin iontophoresis, application current density 2.82 mA/cm2 for 10 min. No increase in corneal thickness was observed, but there was a decrease in the number of corneal cells only after salt iontophoresis and not after gentamicin iontophoresis. Eljarrat-Binstock et al evaluated epithelial defects and stromal edema 5 min after application 2.5–5.1 mA/cm2 current 1–2 min. When using bottom current density for 1 min these findings disappears after 8 hours, while after application a higher current density mild stromal edema is still observed at the 8 hour time point. Transscleral Iontophoresis toxicity was assessed using higher current densities where choroid a retinal damage was observed. Maurice destruction of the retinal layers was detected and resulting in choroidal congestion using transscleral fluorescein iontophoresis current density 127–254 mA/cm2 for 2–5 min. Barza et al assessed tolerance cefazolin and gentamicin iontophoresis for 3 hours after high current density application (254.6, 127.0 and 101.9 mA/cm2) for 5 or 10 min. The animals did not record any evidence discomfort corresponding to all current densities applied with a maximum voltage of
150 V. However, histopathological examination showed hemorrhagic necrosis, edema and infiltration by polymorpho nuclear cells v choroid, retina and ciliary body using 254.6 and 127.0 mA/cm2 for 5 and 10 min. On in another study reported the use of an extremely high current density (765.3 mA/cm2) for 10 minutes, resulting in retinal burns but normal electro-retino grams in monkey for several weeks after several sessions gentamicin

transscleral iontophoresis. Lam etal work on the same problem using application of transscleral iontophoresis of physiological solution and current density 531 mA/cm2. They found that the size and severity of chorioretinal lesions in rabbits, 5 days after treatment, increases with application length (2–25 minutes). No retinal lesions were observed examination with a light microscope, after 1 min iontophoretic treatment. Iontophoretic treatment for 5 and 15 minutes resulted in necrosis retinal pigment epithelium (RPE), proliferation of RPE cells and macrophages activity and loss of retinal nuclear layers which within 14 days resulted in eventual glial membrane. Behar-Cohen scored a no histological damage or signs of thermal damage on the cornea and sclera after application 1.2 mA/cm2 current for 4 minutes using 6 mm the diameter of the orbit covering the cornea a rat sclera. Also when using 4 mA/cm2 for 10 min no visible lesions in the area application, no abnormalities or hist findings were obtained 24 hours later iontophoretic treatment using a ring transscleral device They also announced a safe procedure with lower current intensity than 50 mA/cm2 for transscleral iontophoresis. Voigt, 20, and Kralinger, 51, investigated safety single and repeated transscleral simultaneous aspirin iontophoresis density only 5.0 mA/cm2 for 10 min. Eight hours after a single iontophoretic treatment anterior segment, vitreous cavity and the fundus was examined using a slit lamp biomicroscopy and indirect ophthalmoscopy. No signs of retinal detachment or anything intraocular complications have been observed, apart from a mild conjunctival injection that disappeared after 8 hours. Histologically without signs inflammation or tissue damage observed in anterior or posterior segments eyes . Also after serial iontophoresistreatment at 24-hour intervals for one week, no inflammation or toxicity was demonstrated observed. retinal epithelium, photoreceptors and nuclear layers were not and electroretinographic analysis showed a typical response.

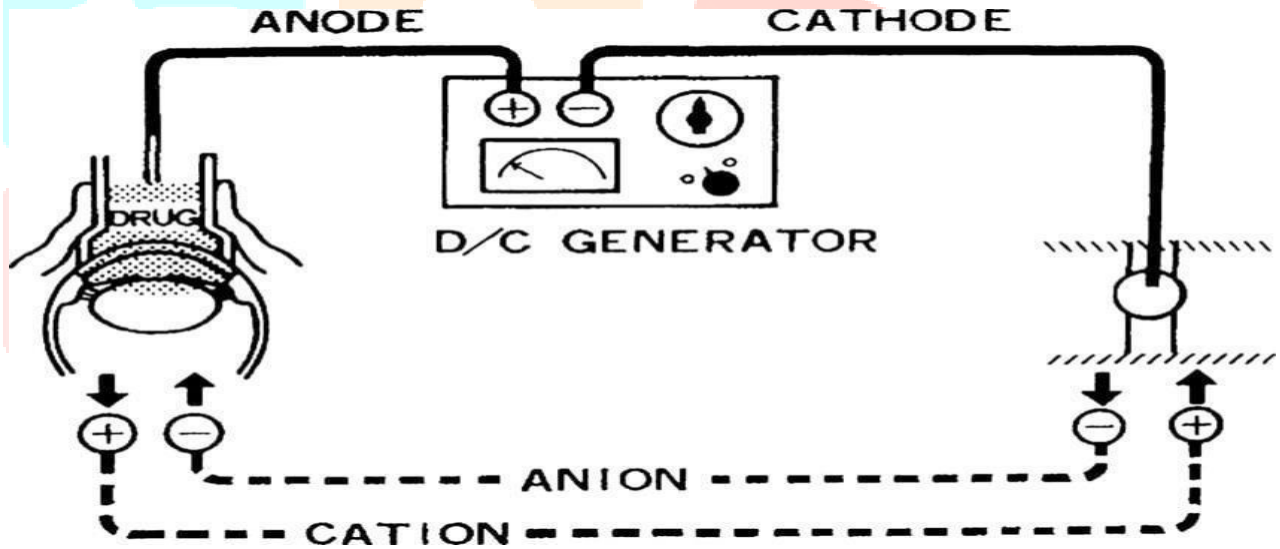


Fig5: Ocular Iontophoresis of positively charged drug

❖ Conclusion:

In the current scenario, ocular iontophoresis proves its clinical potential and importance as local multidrug delivery system. AND better understanding of tissue interactions in the eye with an electric current along with better device design and probes adapted to the application site, provides effective intraocular penetration drugs need to be studied. Technology eye iontophoresis reached up to maturity in terms of equipment development. Iontophoretic treatment is already a promising tool for providing anti inflammatory and antibiotic drugs in the eye. Experiments are needed to determine the ability of these techniques to add variety other chemotherapy agents for treatment other bacterial infections, to determine safety for a long time and on determine efficacy in humans. Eye irritation associated with ocular iontophoresis has beenaddressed by several studies and is a problem preventing widespread use technique. However, steps in development of eye iontophoretics technologies lead to the need for less intense current levels to achieve therapeutic effective drug delivery, and it will dramatically reduce the problem of eye irritation. It is only a matter of time before iontophoresis occurs routinely used in the

eyearea.

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